

## Plasma and tissue digoxin concentrations in patients undergoing cardiopulmonary bypass

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*Plasma, myocardial, and skeletal muscle digoxin concentrations were measured in 32 patients undergoing cardiopulmonary bypass who were on long-term treatment with digoxin. The patients were divided into 4 groups according to their daily digoxin dose and the interval between discontinuation of the drug and operation. Before bypass, the mean digoxin concentrations were 1.58 nmol/l (1.24 ng/ml) in plasma, 65.2 nmol/kg (50.9 ng/g) in the atria, 121.4 nmol/kg (94.8 ng/g) in 11 papillary muscles, and 16.6 nmol/kg (13.0 ng/g) in skeletal muscle. Mean atrial digoxin concentrations were significantly lower than mean papillary muscle concentrations in 11 patients. Ratios of plasma to myocardial or skeletal muscle digoxin concentrations were very variable. Generally digoxin concentrations were higher in patients on the larger digoxin dose and with the shorter discontinuation time before surgery. These differences attained significance only with plasma digoxin concentrations. There was a slight fall in plasma digoxin concentration during cardiopulmonary bypass but no significant differences were observed between plasma, atrial, or skeletal muscle digoxin concentrations before and at the end of bypass. No clear relation was seen between plasma or atrial digoxin concentrations and postoperative cardiotoxicity. Stopping digoxin 48 hours before operation appeared to account for pre- or post-bypass plasma digoxin concentrations of less than 1.0 nmol/l (0.8 ng/ml) in most of the instances encountered, whereas the 3 patients who developed pulsus bigeminus postoperatively had received 0.5 mg digoxin only 24 hours before operation.*

The recent introduction of methods enabling the estimation of plasma digoxin concentrations has contributed significantly to knowledge of the clinical pharmacology of this drug. Therapeutic and toxic ranges of plasma digoxin concentrations have been identified in patients on chronic maintenance doses of digoxin (Smith, Butler, and Haber, 1969; Smith and Haber, 1970; Chamberlain *et al.*, 1970; Evers and Chapman, 1971), though some overlap occurs between the two groups. A surprisingly large proportion of patients admitted to hospital appears to be taking inadequate amounts of digoxin (Carruthers, Kelly, and McDevitt, 1974). Interpretation of plasma digoxin concentrations depends upon the assumption that a relatively constant relation exists between plasma and myocardial receptor site concentrations, since it is the latter (together with the response of the tissue) which ultimately determines the effect of the drug (Smith and Haber, 1972).

The relation between plasma and myocardial tissue digoxin concentrations has been the subject of a number of investigations. Initially Doherty,

Perkins, and Flanigan (1967) suggested that a relatively constant ratio existed between the two, but subsequent investigations have not supported this (Binnion *et al.*, 1969; Coltart, Howard, and Chamberlain, 1972; Carroll *et al.*, 1973) and wide variations in myocardial tissue digoxin concentrations have been reported. Carroll *et al.* (1973) have recently suggested that there is no difference between the atrial and ventricular concentrations of the drug in humans, but this is at variance with results obtained from dogs (Deutscher, Harrison, and Goldman, 1972) and from human necropsy studies after administering radioactive digitoxin (Okita *et al.*, 1955).

The effects of cardiopulmonary bypass on plasma and tissue digoxin levels have also been in dispute. A decrease in myocardial digoxin concentration, accompanied by a rise in plasma digoxin levels, has been reported as a result of bypass in both dogs (Austen *et al.*, 1962) and humans (Ebert, Morrow, and Austen, 1963). Other authors have found, both in animals and man, that there is a significant drop in the plasma digoxin level which is not accom-

panied by a corresponding change in myocardial concentration (Molokhia *et al.*, 1971; Beall *et al.*, 1963). However, the influence of bypass on skeletal muscle digoxin concentration has not been studied, despite the recognition that the storage capacity of this tissue for digoxin is enormous compared to the relatively small quantities of digoxin in plasma, heart, or other tissues (Doherty *et al.*, 1967).

The present study was designed to determine and compare the cardiac, skeletal muscle, and plasma concentrations of digoxin in patients on two chronic dosage regimens, who had their digoxin discontinued at one of two preoperative intervals, and to examine the effects of cardiopulmonary bypass on the digoxin concentrations in these patients.

### Patients and methods

Patients admitted for heart surgery under cardiopulmonary bypass were selected on the basis of their usual daily digoxin therapy. Sixteen patients had taken 0.25 mg daily regularly and another 16 patients had taken 0.5 mg daily. In each dosage group, 8 patients (50%) were given their last preoperative dose of digoxin (Lanoxin, Burroughs Wellcome) 48 hours before surgery while the remainder received their final preoperative dose 24 hours later. Eight male and 24 female patients were studied. Their ages ranged from 30 to 68 years (mean 47 years). Routine investigations on the preoperative day

included serum creatinine, plasma urea, and electrolyte estimation and a 12-lead electrocardiogram.

The operations were performed using conventional bypass techniques with a Rygg-Kyvsgaard<sup>1</sup> bubble oxygenator and Sarns<sup>2</sup> roller pump. The arterial flow was 2.4 l/m<sup>2</sup> body surface area. The oxygenator was primed with 30 to 40 ml/kg of fluid composed of equal amounts of Hartmann's solution and 5 per cent dextrose in water. A further 10 to 15 ml/kg of 5 per cent dextrose in water was infused intravenously during the operation. Fluid composed of equal amounts of blood and Hartmann's solution was added to the oxygenator to maintain its level. Patients received on average 1 litre of blood in theatre.

Samples of blood, right atrial appendage, and pectoralis muscle from the edge of the sternotomy incision were taken just before bypass began. Depending on the duration of bypass, blood samples were taken at 10, 30, 90, and 150 minutes. In addition, samples of papillary muscle were obtained from 11 patients. Further blood, right atrial appendage, and pectoralis muscle samples were taken at the end of bypass, and the duration of extracorporeal circulation was noted.

Carefully prepared fat-free samples of skeletal and cardiac muscle (30–70 mg) were accurately weighed after lightly blotting dry. Digoxin was extracted by homogenizing with 2.5 ml chloroform (Analar grade) on 2 separate occasions and removing the supernatants. The

<sup>1</sup>Rygg Kyvsgaard disposable bubble oxygenator (Polystan, Copenhagen).

<sup>2</sup>Sarns Inc., 6200 Jackson Road, Ann Arbor, Mich., U.S.A.

TABLE I Summary of observations in 32 chronically digitalized patients undergoing cardiopulmonary bypass. Results are expressed as mean  $\pm$  standard deviation. The figures in parentheses indicate the range of results.

Group	Daily digoxin dose (mg)	Pre-op interval without digoxin (hr)	No. of patients	Sex	Age (yr)	K <sup>+</sup> (mmol/l)	Urea (mmol/l)	Creatinine ( $\mu$ mol/l)
A	0.25	24	8	M 2 F 6	47 $\pm$ 19 (34–63)	4.6 $\pm$ 0.8 (3.7–5.6)	6.142 $\pm$ 0.830 (5.312–6.972)	97.2 $\pm$ 26.5 (70.7–114.9)
B	0.25	48	8	M 3 F 5	52 $\pm$ 8 (42–68)	4.2 $\pm$ 0.3 (3.8–4.7)	6.806 $\pm$ 2.158 (4.150–9.794)	88.4 $\pm$ 26.5 (70.7–123.8)
C	0.5	24	8	M 2 F 6	47 $\pm$ 8 (38–56)	4.2 $\pm$ 0.5 (3.3–5.0)	5.644 $\pm$ 1.826 (2.656–8.466)	106.1 $\pm$ 44.2 (70.7–159.1)
D	0.5	48	8	M 1 F 7	43 $\pm$ 11 (30–59)	4.1 $\pm$ 0.3 (3.4–4.6)	5.312 $\pm$ 1.826 (2.324–7.968)	79.6 $\pm$ 26.5 (70.7–106.1)

\* AF = atrial fibrillation; SR = sinus rhythm.

† AVR, MVR, PVR, TVR indicate aortic, mitral, pulmonary, tricuspid valve replacement, respectively.

SI Units to Traditional Units:

Conversion factor—K<sup>+</sup> 1 mmol/l = 1 mEq/l; Urea 1 mmol/l  $\approx$  6 mg/dl; Creatinine 1  $\mu$ mol/l  $\approx$  1.13 mg/dl.

supernatant from a third extraction showed no evidence of digoxin. The first 2 supernatants were mixed and aliquots used for digoxin determination. The digoxin content of plasma and tissue extracts was measured by the radioimmunoassay method of Smith *et al.* (1969) using the Wellcome  $\beta$ -Lanoxitest kit modified according to Ojala, Karjalainen, and Reissell (1972). Tissue concentrations of digoxin were subsequently calculated from knowledge of tissue weights and the amounts of digoxin detected in the supernatants.

Statistical analyses were carried out using Student's *t* test. Differences were considered significant when the probability (*P*) was less than 0.05. All results are expressed as the mean  $\pm$  standard deviation.

### Results

Observations on sex, age, electrocardiographic and biochemical data, operation, and duration of cardiopulmonary bypass are shown in Table 1 for each of the 4 groups of 8 patients, divided according to daily digoxin dosage and drug discontinuation time.

One patient underwent repair of an atrial septal defect and had an aortic homograft valve replacement of the pulmonary valve for a congenital defect, but all other valve replacements were of the Starr-Edwards ball valve type. There was a fivefold variation in the duration of bypass in all subjects (45 to 210 minutes) and a twofold variation in the mean between groups (69 to 120 minutes). The mean

duration of cardiopulmonary bypass for all 32 patients was 95 minutes.

### Plasma and tissue digoxin concentrations and ratios

Plasma, atrial, and skeletal muscle digoxin levels in samples obtained at the onset of bypass are shown in Table 2. At the onset of bypass the digoxin level in plasma for all subjects ranged from 0.4 to 3.7 nmol/l (0.3 to 2.9 ng/ml). Five patients had levels greater than 2.6 nmol/l (2.0 ng/ml) and 7 patients had levels less than 1 nmol/l (0.8 ng/ml). The mean level in all subjects was 1.5 nmol/l (1.2 ng/ml). In patients who stopped digoxin, 0.25 mg daily, 48 hours before operation (Group B), plasma digoxin levels (mean  $1.2 \pm 0.4$  nmol/l ( $0.9 \pm 0.3$  ng/ml)) were significantly lower than in the patients on the same dose whose therapy was stopped 24 hours later (Group A, mean  $1.8 \pm 0.6$  nmol/l ( $1.4 \pm 0.5$  ng/ml)). Patients receiving 0.5 mg daily also had significantly lower plasma digoxin levels when therapy was stopped 48 hours before operation (Group D, mean  $1.2 \pm 0.6$  nmol/l ( $0.9 \pm 0.5$  ng/ml)), than those whose digoxin was stopped only 24 hours before surgery (Group C, mean  $2.2 \pm 0.9$  nmol/l ( $1.7 \pm 0.7$  ng/ml)).

Atrial digoxin levels ranged from 2.9 to 166.7 nmol/kg (2.3 to 130.2 ng/g), with a mean level of 65.2 nmol/kg (50.9 ng/g). The ratio of atrial to plasma digoxin levels ranged from 3.8:1 to 124:1 with a mean ratio of 46.3:1. Skeletal digoxin levels ranged from 2.6 to 93.1 nmol/kg (2.0 to 72.7 ng/g) with a mean level of 16.6 nmol/kg (13.0 ng/g). Fifty per cent of samples contained between 12.8 and 25.6 nmol/kg (10 and 20 ng/g); only 3 patients had skeletal muscle digoxin levels greater than 38.4 nmol/kg (30 ng/g) and only 3 were less than 6.4 nmol/kg (5 ng/g). The mean ratio of skeletal to plasma digoxin concentrations was 13.2:1 with a range from 1.9:1 to 35.3:1.

For each of the doses, the atrial and skeletal muscle digoxin concentrations were higher 24 hours after stopping therapy than after 48 hours, but these differences were not significant.

A sample of papillary muscle was obtained for digoxin assay in 11 patients. Papillary muscle concentrations ranged from 29.6 to 202.7 nmol/kg (23.1 to 158.3 ng/g), with a mean of 121.4 nmol/kg (94.8 ng/g). Papillary/plasma digoxin ratios ranged from 39.3:1 to 114.4:1 with a mean of 70.6:1 (corresponding mean atrial/plasma and skeletal/plasma ratios in this group were 52.2:1 and 15.9:1, slightly higher than in the total group). In these 11 patients, the digoxin levels in papillary muscle were significantly greater than those in atrial muscle,

ECG*	Operation†	Duration of bypass (min)
5 AF	1 AVR 4 MVR	120 $\pm$ 53
3 SR	1 AVR, MVR 1 AVR, MVR, TVR 1 PVR, repair, ASD	(47-216)
7 AF	1 AVR 6 MVR	80 $\pm$ 48
1 SR	1 Mitral valvotomy	(45-199)
6 AF	2 MVR	
2 SR	5 AVR, MVR 1 MVR, TVR	110 $\pm$ 48 (50-210)
6 AF	1 AVR 5 MVR	69 $\pm$ 29
2 SR	1 AVR, MVR 1 MVR, TVR	(51-140)

TABLE 2 Plasma, atrial, and skeletal muscle digoxin concentrations at the beginning and end of cardiopulmonary bypass. Mean  $\pm$  SD in each of 4 groups of 8 subjects

Group	Pre-bypass digoxin concentrations			Post-bypass digoxin concentrations		
	Plasma (nmol/l)	Atrium (nmol/kg)	Skeletal muscle (nmol/kg)	Plasma (nmol/l)	Atrium (nmol/kg)	Skeletal muscle (nmol/kg)
A	1.8 $\pm$ 0.6	61.4 $\pm$ 32.5	17.2 $\pm$ 8.4	1.7 $\pm$ 0.6	60.9 $\pm$ 36.6	13.9 $\pm$ 10.9
B	1.2 $\pm$ 0.4	50.0 $\pm$ 23.4	12.7 $\pm$ 8.4	0.9 $\pm$ 0.4	54.9 $\pm$ 25.1	11.1 $\pm$ 6.1
C	2.2 $\pm$ 0.9	84.5 $\pm$ 20.9	22.5 $\pm$ 15.2	2.4 $\pm$ 1.0	84.7 $\pm$ 21.6	20.7 $\pm$ 14.6
D	1.2 $\pm$ 0.6	64.9 $\pm$ 41.9	14.3 $\pm$ 10.9	1.0 $\pm$ 0.5	55.5 $\pm$ 54.5	13.7 $\pm$ 7.8
All groups	1.5 $\pm$ 4.6	65.2 $\pm$ 185.3	16.6 $\pm$ 65.2	1.5 $\pm$ 4.7	64.0 $\pm$ 203.1	14.9 $\pm$ 59.9

SI Units to Traditional Units: Conversion factor—Digoxin 1 nmol/l  $\approx$  0.78 ng/ml; 1 nmol/kg  $\approx$  0.78 ng/mg

even though 2 patients had atrial concentrations just greater than papillary concentrations.

Assuming an elimination half-life for digoxin of 1.6 days (Jelliffe, 1968), near normal renal function, and that the studies in rats, using tritiated digoxin which showed that decay occurred in all tissues at the same rate (Okita, 1969) are indicative of human tissue response, it is possible to extrapolate the digoxin concentrations found in atrial and skeletal muscle at 24 and 48 hours back to zero-time. This would give mean atrial digoxin concentrations at zero-time of 108.2 nmol/kg (84.5 ng/g) for patients taking 0.25 mg daily and 142.4 nmol/kg (111.2 ng/g) for those taking 0.5 mg daily. The comparable mean digoxin concentrations for skeletal muscle would be 28.3 and 34.4 nmol/kg (22.1 ng/g and 26.9 ng/g) for the two dose levels, respectively.

#### Effects of cardiopulmonary bypass

The mean plasma digoxin levels in each group at the various times of sampling during cardiopulmonary bypass are shown in Table 3. There is a decline in the mean plasma level with an observed minimum between 30 and 90 minutes and a return at the end of bypass to levels which approximate to those found initially. None of these changes reaches statistical significance. The overall mean plasma digoxin levels were 1.5 nmol/l (1.2 ng/ml) (before bypass), 1.4 nmol/l (1.1 ng/ml) (10 min), 1.4 nmol/l (1.1 ng/ml) (30 min), 1.7 nmol/l (1.3 ng/ml) (90 min:  $n=14$ ) and 1.5 nmol/l (1.2 ng/ml) (end of bypass).

Mean plasma, atrial, and skeletal muscle digoxin levels within each group show no significant change after bypass (Table 2). The mean pre- and post-bypass tissue levels are distinctly similar: 1.5 nmol/l and 1.5 nmol/l (1.2 ng/ml and 1.2 ng/ml) respectively for plasma, 65.2 nmol/kg (50.9 ng/g) and 64.0 nmol/kg (50.0 ng/g), respectively, for atrial muscle and 16.6 nmol/kg and 15.0 nmol/kg

(13.0 ng/g and 11.7 ng/g) for skeletal muscle digoxin concentrations. However, within individual patients there were many occasions when plasma and tissue digoxin levels rose or fell appreciably during the bypass procedure. There was a considerable degree of overlap between these patients and there was no clear evidence of any pattern in the changes observed.

#### Postoperative clinical course

Two patients did not achieve adequate cardiac output on termination of bypass and subsequently died in spite of supportive measures. Postoperative plasma digoxin levels in these patients were within the acceptable range at 1.7 and 1.8 nmol/l (1.3 and 1.4 ng/ml), respectively. Their necropsy studies showed considerable myocardial ischaemia. Two patients, who had low preoperative plasma digoxin levels of 0.5 and 0.8 nmol/l (0.4 and 0.6 ng/ml), developed rapid atrial fibrillation within 6 to 8 hours of operation, which responded to further digoxin therapy. Three patients whose plasma digoxin levels at the end of bypass were 1.8, 2.8, and 4.1 nmol/l (1.4, 2.2, and 3.2 ng/ml), subsequently developed runs of pulsus bigeminus. However, 5 patients whose plasma digoxin levels had not been above 0.9 nmol/l (0.7 ng/ml) and 2 patients with post-bypass plasma concentrations of 2.7 and 3.7 nmol/l (2.1 and 2.9 ng/ml) underwent their operations without any postoperative complications. Three patients died within 14 days of the study as a result of thromboembolic complications. This problem has been described elsewhere (Cleland and Molloy, 1973).

#### Discussion

The patients in this study had all been in heart failure and the majority suffered also from atrial

TABLE 3 Plasma levels of digoxin (nmol/l) measured before, during and at the end of cardiopulmonary bypass (mean  $\pm$  SD). Values for 8 subjects except where stated. The mean duration of bypass was  $95 \pm 45$  minutes

Group	Before bypass	10 min	30 min	90 min	End of bypass
A	1.8 $\pm$ 0.6	1.8 $\pm$ 1.2	1.5 $\pm$ 0.8	1.9 $\pm$ 1.2 (n=6)	1.7 $\pm$ 0.6
B	1.2 $\pm$ 0.4	0.9 $\pm$ 0.4	0.9 $\pm$ 0.4	1.5 (n=1)	0.9 $\pm$ 0.4
C	2.2 $\pm$ 0.9	1.9 $\pm$ 1.0	2.0 $\pm$ 1.0	1.8 $\pm$ 0.5 (n=5)	2.4 $\pm$ 1.0
D	1.2 $\pm$ 0.6	1.0 $\pm$ 0.3	0.9 $\pm$ 0.3	0.8 $\pm$ 0.1 (n=2)	1.0 $\pm$ 0.5
All groups	1.5 $\pm$ 4.6	1.4 $\pm$ 5.2	1.4 $\pm$ 4.7	1.7 $\pm$ 3.5	1.5 $\pm$ 4.7

Conversion SI to Traditional Units: Digoxin 1 nmol/l  $\approx$  0.78 ng/ml.

fibrillation (Table 1). Preoperatively, heart rate had been adequately controlled in all cases and clinical signs of heart failure removed by the use of digoxin with addition of a diuretic and potassium supplements in most cases.

The range of pre-bypass plasma digoxin concentrations in the present series is comparable to that reported from similar studies (Coltart *et al.*, 1972; Carroll *et al.*, 1973). However, direct comparisons between different series are difficult because of the variability in, or lack of information about, digoxin dosage regimens and intervals between discontinuation of therapy and sampling blood and tissue digoxin levels. Thus, some authors have neglected to state the usual daily dose and drug discontinuation interval before surgery (Coltart *et al.*, 1972), others have stopped digoxin treatment at the same time in patients receiving different doses (Binnion *et al.*, 1969) or have brought together patients with both different dosage regimens and different intervals between drug discontinuation and operation (Carroll *et al.*, 1973). In these studies, the results were analysed in total groups. While such variations may not affect plasma/tissue digoxin concentration ratios, they will undoubtedly affect the values obtained for individual plasma and tissue digoxin concentrations as is shown in the present study by the results in Table 2.

The atrial digoxin levels in this study ranged from 2.9 to 166.7 nmol/kg (2.3 to 130.2 ng/g), with a mean of 65.2 nmol/kg (50.9 ng/g). These results appear lower than those obtained by Carroll *et al.* (1973), but 16 of their 21 patients were taking digoxin, 0.5 mg daily or greater, and it is not clear how many of these discontinued their therapy only 24 hours before operation. Similarly, higher mean atrial digoxin concentrations have been reported by Binnion *et al.* (1969) using a rubidium-86 red cell uptake method for analysis  $280.4 \pm 53$  nmol/kg

(219  $\pm$  42 ng/g) and by Beall *et al.* (1963) 6 hours after 1 mg tritiated digoxin was given intravenously (140 ng/g).

In 11 patients, papillary muscle concentrations ranged from 29.6 to 202.7 nmol/kg (23.1 to 158.3 ng/g), with a mean of 121.4  $\pm$  53.1 nmol/kg (94.8  $\pm$  41.5 ng/g). This group is undifferentiated for dosage and time interval because of the small numbers involved. It is similar to the range 19.8–169 nmol/kg (15.5–132 ng/g) and mean 99.5  $\pm$  55.4 nmol/kg (77.7  $\pm$  43.3 ng/g) reported for left ventricular papillary muscle digoxin concentrations in 8 patients by Coltart *et al.* (1972).

The similarity between the mean atrial digoxin concentration 97.9 nmol/kg (76.5 ng/g) obtained by Carroll *et al.* (1973) and the mean left ventricular papillary muscle concentration reported by Coltart *et al.* (1972) led Carroll and his colleagues to postulate that there is no difference between atrial and ventricular concentration of the drug in patients on digoxin therapy. However, in our 11 patients, the mean digoxin level in papillary muscle was significantly greater than that in atrial muscle. This finding is in accord with atrioventricular digoxin concentration relations previously demonstrated in animals (Gruber, Luchi, and Turnbull, 1967; Deutscher *et al.*, 1972), in human necropsy material (Okita *et al.*, 1955) and in the patients in this present study who came to necropsy (S. G. Carruthers, J. G. Kelly and D. G. McDevitt, unpublished observations). Why different parts of the myocardium should have distinctly different digoxin concentrations remains uncertain.

Skeletal muscle digoxin concentrations also show a gradient for different dosage levels and time intervals (Table 2). In this case, with the small numbers of patients within the groups, the differences did not attain significance. Extrapolation to zero-time gave mean skeletal muscle digoxin con-

centrations of 28.3 nmol/kg (22.1 ng/g) for patients taking 0.25 mg and 34.4 nmol/kg (26.9 ng/g) for a daily dose of 0.5 mg. Therefore, the possibility exists for differentials between mean skeletal muscle digoxin concentrations attained at different daily digoxin dosages. The ratio of atrial to skeletal muscle digoxin concentrations (about 4:1) is in agreement with that described in dogs given tritiated digoxin intravenously (Deutscher *et al.*, 1972).

In this present study the ratios of plasma digoxin concentrations to the concentrations found in other tissues showed a similar variability to that described by previous authors (Doherty *et al.*, 1967; Binnion *et al.*, 1969; Coltart *et al.*, 1972; Carroll *et al.*, 1973). The range of the ratios for atrial to plasma digoxin concentrations was 2.8:1 to 124:1 (mean 46.3:1), for skeletal muscle to plasma was 1.9:1 to 35.3:1 (mean 13.2:1) and for papillary muscle to plasma digoxin 39.3:1 to 114.4:1 (mean 70.6:1).

Reasons for the observed variability in ratios between plasma and myocardial digoxin have been reviewed by Coltart *et al.* (1972). They suggest that plasma digoxin concentrations may provide a more meaningful index of therapeutic activity than total myocardial concentrations as only about 10 per cent of myocardial digoxin may be bound to active sites (Kuschinsky *et al.*, 1967).

The effect of cardiopulmonary bypass on plasma digoxin concentrations was similar to that shown by Coltart *et al.* (1971). The plasma digoxin levels did not fall as low or remain low for as long as in Coltart's study, but the mean initial plasma digoxin concentration was lower and the mean duration of bypass shorter. A decline in plasma digoxin level was seen as soon as 10 minutes after the institution of bypass and this supports the idea that it probably represents a dilution of the plasma volume by pump and intravenous infusion fluids.

In addition, our findings indicate that there is no appreciable loss of digoxin from the atrial tissue during cardiopulmonary bypass in patients on chronic maintenance digoxin therapy. This is in agreement with the recent study in 8 dogs by Molokhia *et al.* (1971) and the clinical observations of Beall *et al.* (1963). Previously, loss of myocardial digoxin during cardiopulmonary bypass had been reported both in animals (Austen *et al.*, 1962) and in man (Ebert *et al.*, 1963). It now appears, however, that evidence is accumulating for maintenance of digoxin concentration in myocardial tissue during bypass.

In the four groups of patients under study, the skeletal muscle digoxin concentrations fell on average by 0.6 to 3.2 nmol/kg (0.5 to 2.5 ng/g) with an overall mean of 1.7 nmol/kg (1.3 ng/g). The differ-

ence was not significant and may represent variation in the technique or site of sample collection or the experimental error of the quantitation of the skeletal muscle digoxin content. However, if the difference were real and if the skeletal muscle mass amounts to even 40 per cent of body weight, in a 70 kg man a change of 1.7 nmol/kg (1.3 ng/g) in skeletal muscle digoxin concentration would provide 0.05 nmol (0.036 mg) digoxin (or about one-seventh of a 0.25 mg dose) for availability to plasma, myocardium, or other tissue. Coltart *et al.* (1972) showed that a mean total of 0.2 mmol (0.134 mg) digoxin was lost from the urinary tract and a much smaller amount via the oxygenator and discard suction bottle during bypass over an average of 8 hours in 11 patients on maintenance digoxin therapy. They felt that this amount was comparable to the normal urinary digoxin excretion in these people under normal circumstances, but if there were an actual loss of digoxin during bypass, this present study would suggest that restoration of plasma and myocardial digoxin levels could occur with only trivial changes in skeletal muscle digoxin concentrations.

Despite the wide variations between subjects in the levels of digoxin found in the various tissues, there must be a fairly stable relation within each individual as a mere 1 per cent shift of digoxin from skeletal muscle to plasma would produce a 100 per cent increase in plasma digoxin concentration, and a 5 per cent transfer from skeletal muscle to the myocardium would double the cardiac level. Such changes in plasma and cardiac digoxin concentration could be of great importance, yet the changes in skeletal muscle digoxin would be difficult to measure.

The patient undergoing cardiopulmonary bypass appears to be at particular risk if his digoxin dosage is inadequate or excessive. Lack of digitalis predisposes to poor inotropic action at a time when the myocardium has suffered the mechanical injury of surgery, and the poor pump performance may be aggravated by inadequately controlled atrial fibrillation. Metabolic changes may increase myocardial irritability (Pacifico, Digerness, and Kirklin, 1970) thereby accentuating the dangerous arrhythmias of digoxin toxicity. Plasma digoxin concentrations from 1.0–2.6 nmol/l (0.8–2.0 ng/ml) have been described as being within 'the observed "normal" therapeutic range' (Whiting, Sumner, and Goldberg, 1973) for patients with normal renal function on standard daily digoxin dosage. In addition, plasma digoxin levels of 2.6 nmol/l (2.0 ng/ml) or greater demand caution as they are often associated with impending or actual digoxin toxicity.

In the present study, approximately two-thirds of the patients had satisfactory pre-bypass plasma

digoxin levels – consistent with their normal or near normal renal function and relatively young average age group. Five patients had levels greater than 2.6 nmol/l (2.0 ng/ml) before bypass and of these two developed cardiac arrhythmias after surgery; 2 patients developed rapid atrial fibrillation within 6 to 8 hours of operation which responded to further digoxin and both of these came from the group of 7 patients who had pre-bypass plasma digoxin concentrations less than 1.0 nmol/l (0.8 ng/ml). The relation of atrial digoxin concentrations to cardiotoxicity is not clear. Carroll *et al.* (1973) noted serious postoperative complications in 3 of 4 patients with right atrial myocardial concentrations greater than 128 nmol/kg (100 ng/g) but in only 2 of 23 patients with concentrations less than 128 nmol/kg (100 ng/g). However, in the present study the 3 patients who had runs of bigeminy had atrial digoxin concentrations of 85.4, 112.0, and 94 nmol/kg (66.7, 87.5, and 73.7 ng/g), respectively, but no arrhythmia occurred in 10 other patients with post-bypass atrial concentrations ranging from 76.8 to 170.3 nmol/kg (60 to 133 ng/g). Hence knowledge of atrial digoxin concentration does not appear to be of value in the prediction of post-bypass arrhythmias.

The 5 patients whose postoperative complications might definitely be associated with inadequate (2) or excessive digoxin administration (3) had all been on 0.5 mg digoxin daily. The 2 patients who developed fast atrial fibrillation had stopped treatment 48 hours before operation, while the 3 patients who developed pulsus bigeminus had received their last 0.5 mg dose only 24 hours before operation. The group of patients on 0.25 mg daily who stopped treatment for 48 hours before operation included 5 (out of a total of 8) whose post-bypass plasma levels were less than 1.0 nmol/l (0.8 ng/ml), though no evidence of inadequate digoxin treatment developed.

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